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Effects of EMD 15,700 and Disulfiram on Ethanol Intake in Rats Under Schedule-Induced Polydipsia

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ABSTRACT

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Rats received 196 food pellets per day under a fixed-time 90-sec schedule with both 5% (w/v) ethanol and water freely available. More than 80% of the total daily fluid consumption was the 5% ethanol solution. Disulfiram, and a new aldehyde dehydrogenase inhibitor, EMD 15,700, both markedly decreased 5% ethanol intake and slightly increased water intake. These effects lasted for several days. The schedule-induced polydipsia model of ethanol consumption in rats appears to be sensitive to the effects of drugs that inhibit ethanol intake in man.

Key words: ethanol consumption, aldehyde dehydrogenase inhibition, polydipsia

INTRODUCTION

The intermittent delivery of food pellets to the food-deprived rat generates drinking episodes that result in excessive water intake [Falk, 1961]. This phenomenon is generally referred to as schedule-induced polydipsia. Many investigators have used schedule-induced polydipsia to induce rats to drink sufficient ethanol to produce intoxication and/or physical dependence [Falk et al, 1972; Freed, 1972; Freed et al, 1970; Freed and Lester, 1970; Gilbert, 1974; Lester, 1961; McMillan et al, 1976; Meisch and Thompson, 1972].

The purpose of the present experiments was to determine if the schedule-induced polydipsia model of ethanol consumption is sensitive to the effects of drugs used clinically to decrease or eliminate ethanol intake. Disulfiram has been used widely in the treatment of alcoholics [Lundwall and Baekeland, 1971; Fried, 1977]. Disulfiram decreases ethanol intake presumably by inhibiting aldehyde dehydrogenase to increase acetaldehyde levels after ethanol consumption [Kitson, 1977].

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Recently, 1-(4-nitrophenyl)-2-methyl-4-nitro-imidazol (EMD 15,700) also has been reported to be an aldehyde dehydrogenase inhibitor effective in reducing ethanol intake in man [Martin, 1977; Ungethum et al, 1977; Tottmar and Seyfried, 1976]. The present experiments compare the effects of EMD 15,700 and disulfiram on ethanol intake under the schedule-induced polydipsia model.

METHODS

Subjects

The subjects were 18 male Sprague–Dawley rats weighing between 400 and 640 gm with free access to food and water. They were deprived of food until they reached approximately 80% of their free feeding weights. At the beginning of the experiments, the rats also had been water deprived for 24 hours.

Apparatus

The rats were housed in running wheel activity cages (Wahman, Model LC-34). Access to the running wheels was denied in these experiments by keeping the door from the cage compartment to the wheel closed.

At the front end of the cage was a food receptacle (Ralph Gerbrands Co., Model G 7020) into which 97 mg Noyes food pellets could be delivered from a pellet feeder (Ralph Gerbrands Co., Model B-1) mounted atop the cage. Beside each food receptacle, a bottle was mounted with a ball type spout (Wahman, LC-213) extending about 1 cm into the cage. A second bottle and spout were mounted at the rear of the cage in a similar manner. Electromechanical programming and recording apparatus were located in a separate room.

Drug Preparation

Ethanol solution was prepared by diluting absolute ethanol with tap water to a final concentration of 5% (weight/volume). Ethanol was maintained at room temperature.

Disulfiram was suspended in a 2.5% solution of Triton X-100 in distilled water. In order to prevent the drug from precipitating, it was necessary to agitate the suspension constantly while drawing it into the syringe. A 2.5% solution of Triton X-100 also was used as a control injection. All injections were made from a stock of 100 mg/ml. EMD 15,700 was suspended in Tween 80. Tween 80 was used as a control injection. Injection volumes were given on the basis of 0.1 ml/100 gm of body weight. Both drug and control injections were by gavage through an oral feeding needle.

Procedure

Rats were first placed in the Wahman activity cages at 12:00 P.M. The bottle at the front of the cage contained 5% ethanol. The bottle at the rear of the cage was removed. A total of 14 food pellets were delivered 90 seconds apart, 14 times daily, so that a total of 196 food pellets were delivered daily.

After one week, a water bottle was added at the back of the cage. After ethanol and water intake patterns stabilized, usually about 2–3 weeks after addition of the water bottle, gavage of drug or drug vehicle was initiated. Rats were gavaged no more frequently than once weekly and usually there was a longer period between gavages.

Each day between 12:00 and 1:00 P.M., the experimenter entered the test room and weighed the rats and the bottes to determine consumption of water and 5% ethanol. A 1-ml correction was employed for spillage and evaporation. If the rat was to be gavaged, it was done immediately after weighing. Data are reported as milliliters of water or ethanol/100 gm of body weight.

RESULTS

The effects of EMD 15,700 on 5% ethanol and water intake are shown in Figure 1. Under control conditions(eg, for 6 days following oral Tween-80 administration), the rats averaged from 12–14 ml/100 gm of 5% ethanol, which is a daily dose of about 6–7 gm/kg. During the same

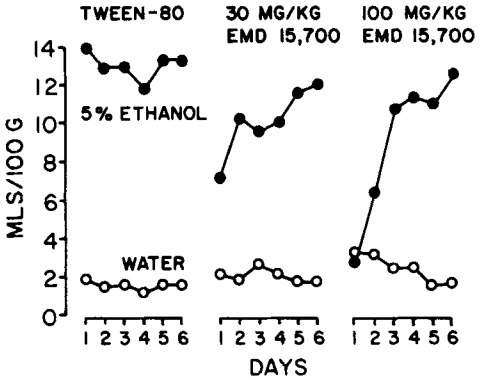

Fig. 1. Effect of EMD 15,700 on 5% ethanol intake and water intake in rats. Ordinate: milliliters of fluid consumed per 100 gm of body weight. Abscissa: days. Filled points show daily ethanol intake and unfilled points show daily water intake. Each point is a mean from six rats.

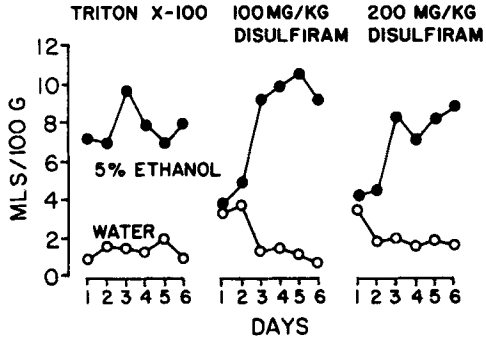

Fig. 2. Effects of disulfiram on 5% ethanol intake and water intake in rats. Ordinate: milliliters of fluid consumed per 100 gm of body weight. Abscissa: days. Filled points show daily ethanol intake and unfilled points show daily water intake. Each point is a mean of three animals.

period, water intake averaged from 1 to 2 ml 100gm/day. Thus the ethanol solution accounted for almost 90% of the fluid intake.

A 30 mg/kg dose of EMD 15,700 reduced 5% ethanol intake to approximately half of the control level during the first 24 hours after its administration. During the next 6 days ethanol intake gradually retured to control level. There was a slight tendency for water intake to be increased over the 6-day period following the 30 mg/kg dose of EMD 15,700. A 100 mg/kg dose of EMD 15,700 markedly reduced 5% ethanol intake and slightly increased water consumption. Recovery of baseline levels of 5% ethanol and water intake again occurred over a 6-day period.

Figure 2 shows similar data on 5% ethanol and water intake for rats exposed to disulfiram. The baseline ethanol intake of these rats (eg, after Triton X-100) was somewhat lower in this group of rats than in the group exposed to EMD 15,700, nevertheless, the effects were strikingly similar. Doses of 100 and 200 mg/kg of disulfiram markedly reduced the intake of 5% ethanol solution and slightly increased water consumption. The effects of disulfiram lasted approximately 48 hours.

It is possible that the effects of EMD 15,700 and disulfiram may have resulted from non-specific behavioral depression, rather than any specific interaction between these drugs and ethanol

intake. To test this possibility, five rats were tested with only water available, rather than with both water and 5% ethanol available. These data are shown in Figure 3.

A dose of 100 mg/kg of EMD slightly increased water intake and a dose of 200 mg/kg of disulfiram had little effect on water intake. These data do not support the idea that ethanol intake was decreased because the drugs suppressed drinking in a nonspecific manner.

The effects of repeated administration of EMD 15,700 also were studied. The first two administrations occurred 3 days apart, after which the drug was given daily for several days. These data are shown in Figure 4.

When 50 mg/kg EMD 15,700 administration was given at 3-day intervals, 5% ethanol intake was reduced by about 50% during the first 24 hours after administration, after which recovery gradually occurred. Daily administration of 50 mg/kg EMD 15,700 reduced 5% ethanol intake to approximately one-third to one-half of control levels for a 5-day period. When the administration of EMD 15,700 was discontinued, ethanol consumption quickly returned to control levels.

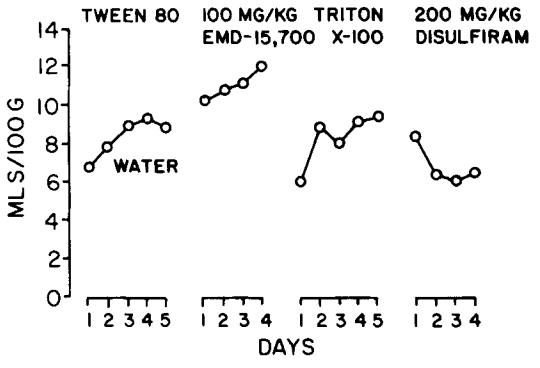

Fig. 3. Effects of EMD 15,700 and disulfiram on water intake with no ethanol available. Ordinate: milliliters of water consumed per 100 gm of body weight. Abscissa: days. Points for Tween 80 and EMD 15,700 are means from five rats and points for Triton-X-100 and disulfiram are means from three rats.

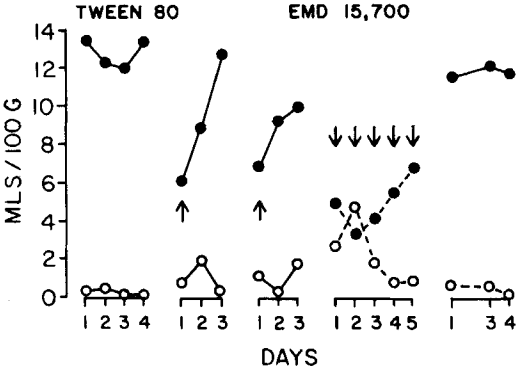

Fig. 4. Effects of repeated administration of EMD 15,700 on 5% ethanol and water intake in rats. Ordinate: milliliters of fluid consumed per 100 gm of body weight. Abscissa: days. Points represent means from two rats. Arrows represent the day following administration of EMD 15,700.

DISCUSSION

The present experiments show that two drugs that inhibit aldehyde dehydrogenase and are used clinically to reduce ethanol consumption, EMD 15,700 and disulfiram, both reduced ethanol consumption in the schedule-induced polydipsia model. It might be argued that the effects of these drugs may not be specific to ethanol drinking, but rather they exert sedative or toxic effects that prevent the consumption of all fluid. Two facts argue against this interpretation. First, reductions in ethanol intake were frequently accompanied by small increases in water intake. Although such data suggest that there was a specific interaction of the drug with ethanol to reduce ethanol intake without reducing water intake, it is clear that total fluid intake was considerably reduced by both drugs since the increased water intake was not sufficient to compensate for the reduced fluid intake produced by the decreased consumption of 5% ethanol. A more convincing argument can be derived from the experiments where ethanol was not involved. Neither EMD 15,700 nor disulfiram reduced water intake when 5% ethanol was unavailable, suggesting that there was a specific interaction between ethanol consumption and the drugs which resulted in decreased ethanol consumption.

Both EMD 15,700 and disulfiram markedly reduced ethanol consumption for 1–2 days after administration, although smaller effects on ethanol drinking were sometimes seen for as long as 6 days. When EMD 15,700 was given daily, it was possible to maintain a large reduction of ethanol consumption as long as the drug administration continued. These data suggest that the repeated drug administration was not producing a lasting conditioned aversion to ethanol consumption that continued after the short period of five daily administrations of EMD 15,700. Each day the animals continued to drink some ethanol despite the administration of EMD 15,700 and when the administration of EMD 15,700 was discontinued, the rats quickly resumed drinking of 5% ethanol solution at the usual rate.

Relative to disulfiram, EMD 15,700, is a comparatively new drug. It appears to be more potent than disulfiram as an aldehyde dehydrogenase inhibitor and has a faster onset of action than disulfiram. EMD 15,700 differs from disulfiram in that it does not appear to inhibit dopamine-β-hydroxylase [Kaser et al, 1976; Seyfried et al, 1981), which might result in less cardiovascular and sedative side-effects with EMD 15,700 than with disulfiram. In the schedule-induced polydipsia model EMD 15,700 appeared to have efficacy approximately equivalent to that of disulfiram and also was more potent.

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